REMARKS

Previously, Claims 7-9 and 11 are pending and under consideration. The Patent Office has indicated that Claims 7-9 are allowable. In the instant amendments, Claim 11 has been amended. Claim 12 has been added. After entry of the instant amendments, Claims 7-9, 11 and 12 will be pending and under consideration.

I. AMENDMENTS TO THE CLAIMS

Claim 11 has been amended. Support for the amendment to Claim 11 can be found, for example, in the specification at page 5, lines 28-30, page 6, lines 5-12, and page 14, lines 25-36.

Claim 12 has been added. Support for the claim can be found, in the specification, for example, at page 2, lines 13-23, at page 5, lines 21-23, at page 13, line 12, to page 14, line 24, at page 19, lines 33-36, and at page 20, lines 20-29.

As the amendments do not introduce any new matter and are fully supported by the specification of the present application, entry and consideration thereof is respectfully requested.

No amendment fee is believed to be due.

II. REJECTION OF CLAIM 11 UNDER 35 U.S.C. § 103(a)

Claim 11 stands rejected under 35 U.S.C. § 103(a) as allegedly being obvious over either U.S. Patent No. 6,025,130 to Thomas *et al.* ("the '130 patent") or U.S. Patent No. 6,140,305 to Thomas *et al.* ("the '305 patent"). Applicants respectfully traverse the rejection of Claim 11.

A. Legal Standard

To reject claims in an application under 35 U.S.C. § 103, the Patent Office bears the initial burden of establishing a *prima facie* case of obviousness. *In re Bell*, 26 U.S.P.Q.2d 1529, 1530 (Fed. Cir. 1993); M.P.E.P. § 2142. In the absence of establishing a proper *prima facie* case of obviousness, applicants who comply with the other statutory requirements are entitled to a patent. *In re Oetiker*, 24 U.S.P.Q.2d. 1443, 1444 (Fed. Cir. 1992). In order to establish *prima facie* obviousness, three basic criteria must be met.

First, the prior art, either alone or in combination, must teach or suggest each and every limitation of the rejected claims. *In re Gartside*, 53 U.S.P.Q.2d 1769 (Fed. Cir. 2000).

The teaching or suggestion must be found in the prior art and not based on Applicant's disclosure. *In re Vaeck*, 947 F.2d 488, 20 U.S.P.Q..2d 1438 (Fed. Cir. 1991).

Second, the prior art must provide one of ordinary skill in the art with a suggestion or motivation to modify or combine the teachings of the references relied upon by the Patent Office to arrive at the claimed invention. When an obviousness determination relies on one reference, there must be suggestion or motivation to modify the teaching of the reference in the manner suggested by the Patent Office. *In re Grabiak*, 226 U.S.P.Q. 870 (Fed. Cir. 1985). The suggestion or motivation to combine the references generally arises in the references themselves, but may also be inferred from the nature of the problem or occasionally from the knowledge of those of ordinary skill in the art. *WMS Gaming Inc. v. International Game Technology*, 51 U.S.P.Q.2d 1385, 1397 (Fed. Cir. 1999). The mere fact that references could be modified or combined does not render the resultant modification or combination obvious unless the prior art also suggests the desirability of the modification or combination. *In re Mills*, 16 U.S.P.Q.2d 1430 (Fed. Cir. 1990); M.P.E.P. § 2143.01.

Third, the prior art must provide one of ordinary skill in the art with a reasonable expectation of success. Thus, the skilled artisan, in light of the teachings of the prior art, must have a reasonable expectation that the modification or combination suggested by the Patent Office would succeed. *In re Dow*, 5 U.S.P.Q.2d 1529, 1531-32 (Fed. Cir. 1988). If any one of three criteria are not met, *prima facie* obviousness is not established. *In re Grabiak*, 226 U.S.P.Q. 870 (Fed. Cir. 1985).

B. <u>The Patent Office Has Failed to Establish a *Prima Facie* Case of Obviousness</u>

Applicants respectfully submit that neither reference cited by the Patent Office is sufficient to establish a *prima facie* case of obviousness against Claim 11 as amended.

Applicants submit that neither the '130 patent nor the '305 patent teaches or suggests each and every element of amended Claim 11. For example, neither patent teaches or suggests a HFE polypeptide in a <u>soluble complex</u> with human β_2-microglobulin (β_2m) suitable for administration to a subject. The instant application teaches that the HFE polypeptide of SEQ ID NO:2, containing the H63D mutation, was expressed and secreted as H63D-HFE/β_2m heterodimers in the form of soluble complexes. *See, e.g.*, page 14, lines 25-36, page 20, lines 2-23, and page 21, line 31 to page 22, line 27. As understood by one skilled in the art, secreted proteins are soluble in aqueous solvents even in the absence of

lipids or detergents. *See* Alberts *et al.*, 3d ed. 1994, *Molecular Biology of the Cell*, 626-27 (provided herewith as Exhibit A).

In contrast, the full length HFE polypeptide discussed in the cited documents is an integral membrane protein having a transmembrane domain and requiring detergents to remain in solution as discussed, for example, in the '305 patent at column 24, lines 18-23, as well as in the instant specification at page 7, lines 20-25. The '305 patent describes using β_2m for affinity chromatography of HFE polypeptide, that is, where β_2m is attached to an inert matrix. *See* '305 patent at column 24, lines 25-48. Thus, the '305 patent does not teach or suggest a H63D-HFE polypeptide in a soluble complex with a full length, wide type human β_2m suitable for administration to a subject. For the same reason, the '130 patent does not teach or suggest a soluble complex with a full length, wild type human β_2m.

In view of foregoing, Applicants submit that the Patent Office has failed to establish that the cited references teach or suggest each and every element of amended Claim 11.

In addition, Applicants respectfully submit that it is the teaching of the instant specification that demonstrates that soluble forms of HFE and β_2m complexes have useful effects. *See* page 29, line 20, to page 23, line 6. The '130 patent and '305 patent cited by the Patent Office each disclose that immobilized β_2m can be used for purifying HFE. Applicants respectfully disagree with the Patent Office that there is a reasonable expectation of success of achieving amended Claim 11 by substituting chromatography buffers in the HFE affinity purification procedures disclosed in the cited patent documents, as this would not achieve a soluble form of a H63D-HFE/β_2m complex. Moreover, the Patent Office has not provided a suggestion or motivation to modify the teaching of the cited documents, for example, to achieve a soluble H63D-HFE/β_2m complex suitable for administration to a human.

Accordingly, Applicants respectfully request that the rejection of Claim 11 under 35 U.S.C. § 103(a) be withdrawn.

Applicants respectfully submit that new Claim 12, reciting, *inter alia*, a composition comprising an isolated HFE polypeptide comprising the amino acid sequence of SEQ ID NO:1 in a soluble complex with a full length, wild-type human β_2m, is patentable under 35 U.S.C. § 103(a), for reasons similar to those as explained above with respect to amended Claim 11.

CONCLUSION

In light of the above amendments and remarks, Applicants respectfully request that the Examiner reconsider this application with a view towards allowance.

No fees are believed to be due. However, the Commissioner is hereby authorized to charge any required fee, fee under 37 C.F.R. § 1.17, any underpayment of fees, or credit any overpayment to Jones Day Deposit Account No. 50-3013 in connection to this Amendment and Response.

Respectfully submitted,

Date: AUGUST 12, 2005

54,398

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THIRD EDITION

Bruce Alberts • Dennis Bray
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Front cover: The photograph shows a rat nerve in culture. It is labeled (*yellow*) with a fluoresc antibody that stains its cell body and dendritic processes. Nerve terminals (*green*) from other neurons (not visible), which have made synaps the cell, are labeled with a different antibody. (Courtesy of Olaf Mundigl and Pietro de Camill

Dedication page: Gavin Borden, late president of Garland Publishing, weathered in during his mid-1980s climb near Mount McKinley with MBoC author Bruce Alberts and famous mount guide Mugs Stump (1940–1992).

Back cover: The authors, in alphabetical order, crossing Abbey Road in London on their way t Much of this third edition was written in a hou around the corner. (Photograph by Richard Oli

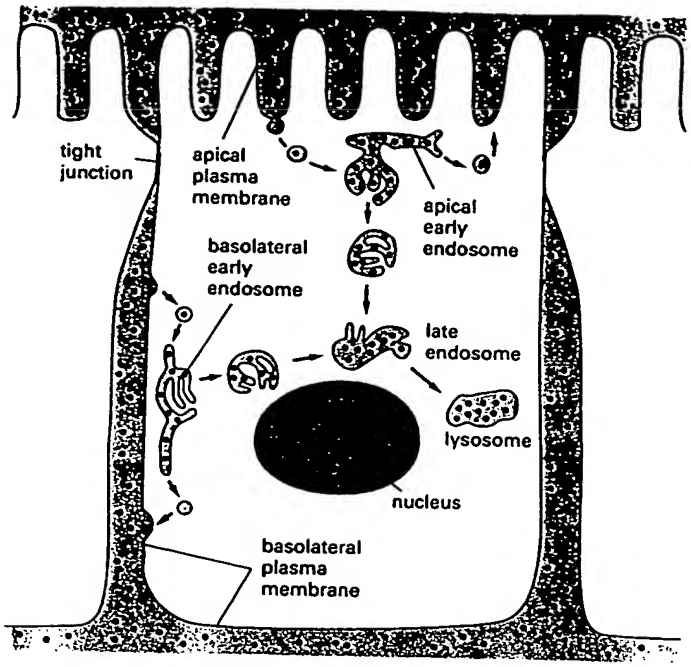
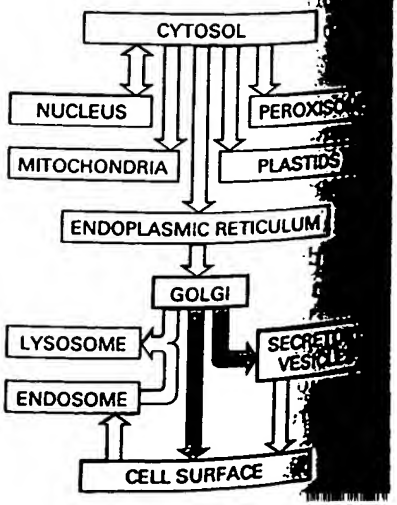


Figure 13–35 Two distinct early endosomal compartments in an epithelial cell. The basolateral and the apical domain of the plasma membrane communicate with distinct early endosomal compartments, although endocytosed molecules from both domains that do not contain signals for recycling or transcytosis meet in a common late endosomal compartment before being digested in lysosomes.

Summary

Cells ingest macromolecules by endocytosis, in which localized regions of the plasma membrane invaginate and pinch off to form endocytic vesicles; many of the endocytosed particles and molecules end up in lysosomes, where they are degraded. Endocytosis occurs both constitutively and as a triggered response to extracellular signals.

Endocytosis is so extensive in many cells that a large fraction of the plasma membrane is internalized every hour. The plasma membrane components (proteins and lipids) are continually returned to the cell surface in a large-scale endocytic-exocytic cycle that is largely mediated by clathrin-coated pits and vesicles. Many cell-surface receptors that bind specific extracellular macromolecules become localized in clathrin-coated pits and consequently are internalized in clathrin-coated vesicles—a process called receptor-mediated endocytosis. The coated endocytic vesicles rapidly shed their clathrin coats and fuse with early endosomes. Most ligands dissociate from their receptors in the acidic environment of the endosome and eventually end up in lysosomes, while most receptors are recycled via transport vesicles back to the cell surface for reuse. But receptor-ligand complexes can follow other pathways from the endosomal compartment. In some cases both the receptor and the ligand end up being degraded in lysosomes, causing "receptor down-regulation." In other cases both are transferred to a different plasma membrane domain, and the ligand is consequently released by exocytosis at a surface of the cell different from that where it originated—a process called transcytosis.



Transport from the *Trans* Golgi Network to the Cell Surface: Exocytosis [29]

Having considered the cell's internal digestive system and the various types of incoming membrane traffic that converge on lysosomes, we now return to the Golgi apparatus and examine the secretory pathways that lead out to the cell exterior. Transport vesicles destined for the plasma membrane normally leave the *trans* Golgi network in a steady stream. The membrane proteins and the lipids in these vesicles provide new components for the cell's plasma membrane, while the soluble proteins inside the vesicles are secreted to the extracellular space. The fusion of the vesicles with the plasma membrane is called **exocytosis.** In this way,

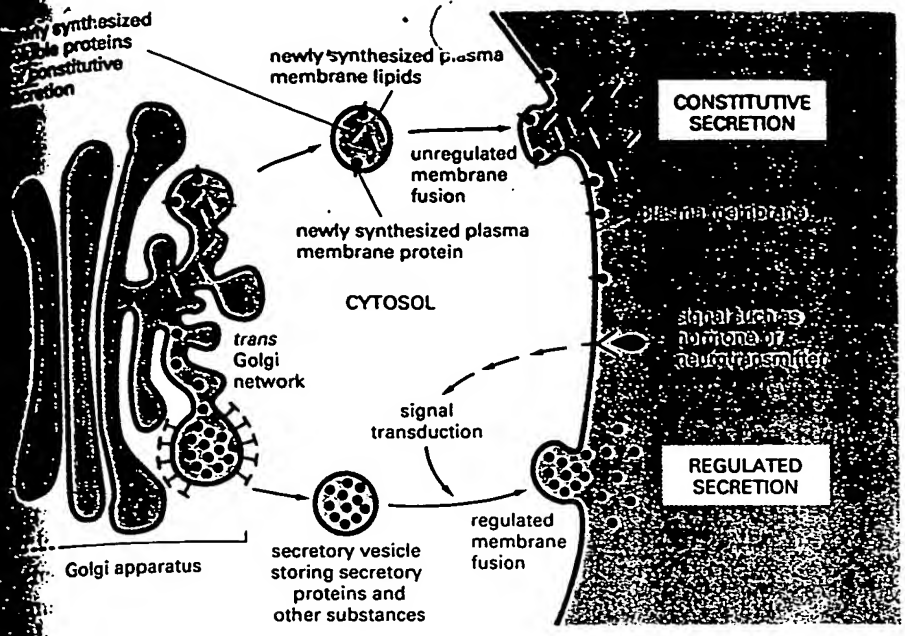


Figure 13–36 The regulated and constitutive secretory pathways. The two pathways diverge in the *trans* Golgi network. Many soluble proteins are continually secreted from the cell by the *constitutive secretory pathway* (also called the *default pathway*), which operates in all cells. This pathway also supplies the plasma membrane with newly synthesized lipids and proteins. Specialized secretory cells also have a *regulated secretory pathway*, by which selected proteins in the *trans* Golgi network are diverted into secretory vesicles, where the proteins are concentrated and stored until an extracellular signal stimulates their secretion. The regulated secretion of small molecules, such as histamine, occurs by a similar pathway: these molecules are actively transported from the cytosol into preformed secretory vesicles. There they are often complexed to specific macromolecules (proteoglycans in the case of histamine), so that they can be stored at high concentration without generating an excessively high osmotic pressure.

for example, cells produce and secrete most of the proteoglycans and glycoproteins of the *extracellular matrix*, which is discussed in Chapter 19.

All cells require this **constitutive secretory pathway.** Specialized secretory cells, however, have a second secretory pathway in which soluble proteins and other substances are initially stored in *secretory vesicles* for later release. This is the **regulated secretory pathway,** which is found mainly in cells that are specialized for secreting products such as hormones, neurotransmitters, or digestive enzymes rapidly on demand (Figure 13–36). In this section we consider the role of the Golgi apparatus in the two secretory pathways and compare the two mechanisms of secretion.

Many Proteins and Lipids Seem to Be Carried Automatically from the ER and Golgi Apparatus to the Cell Surface [30]

In a cell capable of regulated secretion, at least three classes of proteins must be separated before they leave the *trans* Golgi network—those destined for lysosomes (via late endosomes), those destined for secretory vesicles, and those destined for immediate delivery to the cell surface. We have already noted that proteins destined for lysosomes are tagged for packaging into specific departing

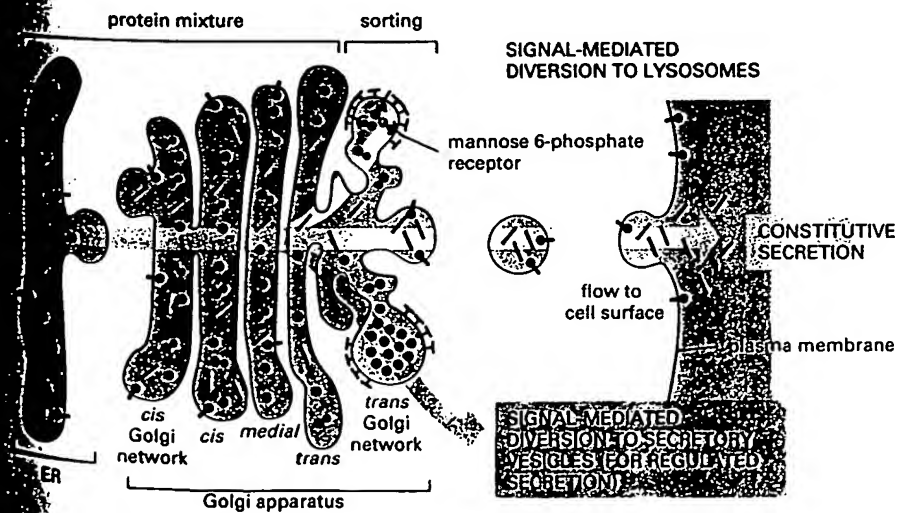


Figure 13–37 The best-understood pathways of protein sorting in the *trans* Golgi network. Proteins with the mannose 6-phosphate marker are diverted to lysosomes (via late endosomes) in clathrin-coated transport vesicles (see Figure 13–23). Proteins with signals directing them to secretory vesicles are concentrated in large clathrin-coated vesicles that rapidly lose their coats to become secretory vesicles—a pathway that is present only in specialized secretory cells. In unpolarized cells proteins with no special features are thought to be delivered to the cell surface by default via the constitutive secretory pathway. In polarized cells, however, secreted and plasma membrane proteins are selectively directed to either the apical or the basolateral plasma membrane domain, so that at least one of these two pathways must be mediated by a specific signal, as we discuss later.